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Fluorous Chemistry in Pittsburgh: 1996–2008[†]

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Abstract

The article summarizes a lecture presented at the American Chemical Society Symposium for the 2008 Award for Creative Work in Fluorine Chemistry on April 7, 2008. A high level, historical overview of work in the fluorous field at the University of Pittsburgh is presented.

In 1994, the journal *Science* published a seminal paper by István Horváth and Josef Rábai on fluorous biphasic catalysis.ⁱ That article and the associated commentary by John Gladyszⁱⁱ inaugurated the field of fluorous chemistry. Coincidentally, we were already thinking about using fluorinated solvents for some tin hydride extractions, and these publications encouraged us to move our nascent ideas from pen and paper into the lab.

Dr. Sabine Hadida undertook the challenge to prepare and study the reactions and separations of a fluorous tin hydride, and her preliminary work appeared in our first paper dealing with fluorous chemistry in 1996.ⁱⁱⁱ The field of combinatorial chemistry was dawning during this period, and Dr. Hadida used her fluorous tin hydride to conduct in parallel a series of nine Giese reactions, as summarized in Figure 1. The tin hydride was used as a catalyst (10 mol%), and sodium cyanoborohydride was the terminal reductant. The reactions were run with benzotrifluoride (BTF) as a cosolvent to promote the solubility of all components. Following evaporation of the solvents (also removed the excess alkene), the crude products were partitioned in a three-phase extraction between water (contains salts), dichloromethane (contains the target products) and FC-72 (perfluorohexanes; provides the recovered tin hydride catalyst). The product yields and purities were highly satisfactory, especially considering the ease of the experiments.

This paper provided the first examples of fluorous tin reagents, introduced the use of “hybrid” solvents like benzotrifluoride^{iv} (now usually called “amphiphilic” solvents), and provided the first examples of triphasic (fluorous/organic/aqueous) extractions. Reactions with amphiphilic solvents and triphasic reactions have since been extensively developed, and are now standard methods in fluorous chemistry. However, in these early days, members of the community (including reviewers of papers) were skeptical of the results. How could Sabine Hadida’s tin hydride, itself an organic compound, be easily and completely extracted out of an organic solvent? The reviewers of our 1996 *JACS* paper asked for proof of the extraction results by ¹⁹F NMR, so Sabine Hadida recorded the ¹⁹F NMR spectra of her nine library products.

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Dedicated to István Horváth, Josef Rábai and John Gladysz

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Since the fluororous tin products had all been removed by extraction, she obtained nine ^{19}F NMR spectra of nothing, except baseline and the reference standard. One of these resonance-free spectra is enshrined in the Supporting Information of the paper³

At this early stage, the field of fluororous chemistry was wide open—almost nothing had been done, but we and a few others had visions. We focused our efforts on more innovative developments rather than low-hanging fruit. In a 1997 *Science* paper, we introduced the concept of “fluororous synthesis” (Figure 2).^v Here we drew the analogy between attaching organic molecules to polymers (solid phase synthesis) and attaching them to fluororous groups (fluororous synthesis). At the same time, we stressed the differences between solid phase synthesis (materials chemistry) and fluororous synthesis (molecular chemistry). Meanwhile, the term “fluororous synthesis” has since evolved to encompass essentially all fluororous methods of synthesis, and the technique of making substrates fluororous is now more commonly called “fluororous tagging” or “fluororous protection”. Though fluororous tags were the first tags for solution phase organic synthesis, we pointed out that the concept of separation tagging for solution phase synthesis was a general one,^{vi} and many other classes of separation tags have since been introduced.^{vii}

During this work, we also encountered difficulties in extracting large organic molecules into fluororous solvents. This led us to test fluororous silica gel for separation, and in 1997 we introduced the technique of fluororous solid phase extraction (FSPE) in a short Note in *J. Org. Chem.*^{viii} This technique is now widely used, and its availability soon led to the sprouting of a light fluororous chemistry branch^{ix} alongside the existing (and still rapidly growing) heavy fluororous branch. The FSPE separation (Figure 2) allow the uses of much smaller (and therefore lighter) fluororous tags, and the method is especially useful for small scale discovery chemistry and library applications in drug discovery and other areas. A recent review of FSPE features almost one hundred papers that have used the technique.^x We and others have introduced scores of light fluororous reagents and protecting groups, and representative assortment of light fluororous protecting groups is shown in Figure 3.

The fast pace of developments continued in the late 1990's as we introduced, among other things, the combination of microwave chemistry (fast reactions) with fluororous tagging (fast separations),^{xi} fluororous reactions in supercritical carbon dioxide,^{xii} fluororous carbohydrates,^{xiii} fluororous chromatography,^{xiv} and fluororous solid-liquid biphasic reactions.^{xv}

In 2000, we started Fluororous Technologies, Inc.^{xvi} with the goal of providing reagents and technological expertise in fluororous chemistry to the community at large. Figure 4 encapsulates the development of the company, which parallels the development of the field. I know that the employees of FTI, past and present, are especially proud to have played a key support role in many fluororous developments throughout the world. Beyond that, the company has contributed with cutting edge research in reagents and separations, library synthesis, peptide chemistry, bi-and triphasic reactions, microarrays, and much more.

The turn of the millennium witnessed continued rapid developments with the use of fluororous BINOLs,^{xvii} the union of fluororous tagging and solid phase synthesis (by the group of Peter Wipf^{xviii}), the beginnings of fluororous peptide chemistry,^{xix} and the introduction of fluororous triphasic reactions.^{xx} In a 2001 *Science* paper, we introduced “fluororous mixture synthesis”,^{xxi} a technique that we have since used in many new guises. The underlying concepts behind fluororous mixture synthesis, Figure 5, are those of solution phase mixture synthesis with separation and identification tagging. These concepts are general, and Craig Wilcox introduced a new class of oligoethylene (OEG) tags.^{xxii}

In 2002, we detailed the principles of fluororous quasiracemic synthesis^{xxiii} and soon after we introduced the concept of complete stereoisomer libraries^{xxiv} (made by fluororous mixture

synthesis), a concept that has been featured in much of our natural products work since then. We later united fluororous and OEG tags in the technique of double mixture synthesis.^{xxv} These techniques have gone well beyond “proof-of-principle”; the derived products (see Figure 6) have been used to solve structure problems and provide importance biological information.^{xxvi} Then in 2004/2005 we introduced the concepts of solvent tuning with hydrofluoroethers (HFE) solvents,^{xxvii} and the technique of fluororous reverse solid phase extraction.^{xxviii}

During the 2002–2004 timeframe, it was also becoming clear that the fluororous field had grown to a critical mass of research groups, as illustrated by the publication in 2002 of the first journal volume dedicated to fluororous papers (a *Tetrahedron* Symposium-in-Print, which provided the modern definition of “fluororous”^{xxix}), and by the convening in 2003 of the first scientific meeting devoted entirely to fluororous chemistry (a symposium sponsored by the Noguchi Institute in Tokyo). In 2004, the first book-length treatment of the field, “The Handbook of Fluororous Chemistry”, was published by Wiley-VCH (Figure 7).^{xxx} With three coeditors and dozens of chapter coauthors, the book well reflected both the breadth and depth of the field at the time.

The first meeting of the fledgling International Society of Fluororous Technologies (ISoFT-1) convened with about 90 enthusiastic participants in Bordeaux in 2005,^{xxxi} the second meeting took place in Yokohama in 2007,^{xxxii} and the third is slated to be held in Pittsburgh in 2009.

One of the most enjoyable aspects of our research in fluororous chemistry has been the people. Sabine Hadida was the first of over 50 coworkers to have worked in ours lab in Pittsburgh on fluororous chemistry. Much of research work has also been driven by enjoyable collaborations with people like Eric Beckman (Pittsburgh, reactions in CO₂), Paul Knochel (Munich, fluororous chromatography), Anders Hallberg and Mats Larhed (Uppsala, microwave chemistry), Roger Read (Sydney, amino acids), Ilhyong Ryu and Hiroshi Matsubara (Osaka, tin reagents, triphasic and phase vanishing^{xxxiii} reactions), Seiji Takeuchi (Niigata, chiral catalysts), Hiroyuki Nakamura (Tokyo, triphasic reactions), Koichi Mikami (Tokyo, fluororous racemic mixture synthesis^{xxxiv}), Peter Wipf (Pittsburgh, fluororous tagging), Craig Wilcox (Pittsburgh, double mixture synthesis), Tadamichi Nagashima, (FTI, reagents) and Marvin Yu (FTI, solvent tuning). The independent group of Wei Zhang at Fluororous Technologies has been especially productive in fluororous library methods and allied techniques,^{xxxv} and I’ve been pleased to be associated with some of their projects.

I warmly thank this excellent cadre of collaborators and coworkers for the intellectual and experimental contributions as well as for their support and friendship. I thank the Institute of General Medical Sciences of the National Institutes of Health for sustained funding of our work in fluororous chemistry over more than a decade. I am also most grateful to the American Chemical Society Division of Fluorine Chemistry for their recognition of our work with the ACS Fluorine Chemistry Award.

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R ¹ : E	CN	CO ₂ Me	COMe
C ₁₅ H ₃₁	72%	92%	67%
<i>n</i> -C ₆ H ₁₁	75%	65%	75%
Ad	89%	94%	78%

- Excess alkene evaporates
- Product in organic liquid phase
- Salts in water phase
- Tin hydride in fluorous phase

Figure 1.
Giese Reactions with a Fluorous Tin Hydride

Compounds for fluorous synthesis have removable (temporary) fluorous tags

Figure 2.
Fluorous Synthesis (left) and Fluorous Solid Phase Extraction (right)

Figure 3.
Representative Fluorous Protecting Groups

- Advanced separation for life sciences**

MEDICINAL CHEMISTRY

DISCOVERY & SCALEUP

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New alternative to solid phase

Affinity tags (protecting groups)

Synthesis reagents

Protein & oligo purification tools

Scavengers

Peptide reagents

Custom fluoros

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Figure 5.
Fluorous Mixture Synthesis

Figure 6.
Natural Products Made by FMS

The author with John Gladysz (left) and István Horváth (center), 2004

Figure 7.
The Handbook of Fluorous Chemistry, 2004